Ultrasonographic Evaluation of the Change in Uterine Fibroids Induced by Treatment with a GnRH Analog

Chun-Chieh Chia*, Soon-Cen Huang, Shen-Shien Chen[1], Jye-Yi Kang[1], Jing-Chuan Lin[1], Yuen-Shan Lin[1], Kuo-Feng Huang[1], Hung-Jung Lee[1], Ching-Cheng Zheng[2]

Department of Obstetrics and Gynecology, Chi Mei Hospital, Liouying, Departments of [1]Obstetrics and Gynecology, and [2]Pathology, Chi Mei Medical Center, Tainan, Taiwan.

SUMMARY

Objective: To investigate the change in volume of uterine fibroids after GnRH analog (GnRHa) treatment.
Materials and Methods: Twenty-five patients who had a uterine leiomyoma were included in this study. Four of them were lost to follow-up during the study, and a myomectomy was performed on the remaining subjects. All of these patients received two doses, 4 weeks apart, each of 3.75 mg leuprorelin acetate subcutaneously (Leuplin depot, a GnRHa) before the operation. The vascularization index (VI), flow index (FI), vascularization–flow index (VFI), pulsative index (PI), resistance index (RI), vascular patterns (histogram), blood flows, and sizes (volume and largest diameter) of each fibroid were measured with power Doppler by the same technician every month before the operation. In addition, the total blood loss and time required for each operation were also recorded.
Results: Results of this study showed that the volume of the uterus and the fibroids, but not the vascularity, including VI, FI, VFI, PI and RI, decreased significantly after two doses of GnRHa treatment. In addition, blood loss during the operation decreased significantly compared to an untreated group.
Conclusion: We found that the volumes of the uterus and fibroids decreased significantly after treatment with two consecutive doses (given a month apart) of GnRHa. The 3D color Doppler including a histogram and blood flow parameters is another useful tool for fibroid evaluation. [*Taiwanese J Obstet Gynecol* 2006;45(2):124–128]

Key Words: GnRH analog, uterine fibroid

Introduction

Uterine fibroids are the most common benign gynecologic tumor and account for more than 80% of gynecologic operations. To preserve the uterus, a combination of medical and surgical management was created such as GnRH analog (GnRHa) treatment before the operation. The aim of this prospective study was to determine the effects of GnRHa on uterine fibroids, as well as on other new parameters including vascularity, for the evaluation and management of fibroids. From these results, we evaluated the possible mechanisms causing fibroid shrinkage.

Materials and Methods

We chose 25 patients who had uterine fibroids, with or without clinical symptoms and signs, for this prospective study. Each of them received 3D power Doppler ultrasound (MEDISON 530D, Korea) before medication and surgery for the following parameters: for fibroids, the size, volume, and blood flow patterns on the histogram including the vascularization index (VI), flow index (FI), and vascularization–flow index (VFI) were evaluated; and for the uterus, uterine arterial blood flow as indicated by the pulsative index (PI) and resistance index (RI) was determined. The VI was

Correspondence to: Dr Chun-Chieh Chia, Department of Obstetrics and Gynecology, Chi Mei Hospital, 201 Taikang, Liouying, Tainan, Taiwan.
E-mail: chia007@iris.seed.net.tw
Accepted: November 21, 2005

Table 1. Volume of uterine and fibroid by ultrasound before and after GnRHa treatment

Pre-vol (ut)	Post-vol (ut)	Diff. ut	Pre-vol (F)	Post-vol (F)	Diff. F
281.4	208.6	–72.8	143.8	124.7	–19.1
449.1	256.8	–192.9	295.9	109.0	–186.9
158.7	106.9	–51.8	29.5	10.8	–18.7
561.3	430.9	–130.4	193.0	212.3	19.3
189.1	195.8	6.7	98.8	126.9	28.1
372.9	357.3	–15.6	178.4	139.8	–38.6
481.5	309.7	–171.8	329.0	176.7	–152.3
169.7	139.7	–30.0	29.0	27.4	–1.6
757.5	598.7	–158.8	479.8	335.6	–144.2
355.3	364.4	9.1	214.2	165.1	–49.1
201.4	111.0	–90.4	134.6	21.3	–113.3
363.1	363.5	0.4	269.6	280.7	11.1
167.6	133.0	–34.6	181.9	82.3	–99.6
787.6	859.3	71.7	450.8	542.7	91.9
351.2	147.1	–204.0	56.6	40.4	–16.2
1,613.7	721.5	–892.2	829.7	363.2	–466.5
303.3	289.3	–14.0	208.7	150.3	–58.5
236.5	208.5	–27.9	102.9	107.1	4.3
298.8	371.1	72.3	166.0	181.3	15.3
971.9	990.3	18.3	882.1	709.6	–172.5
245.7	111.2	–134.5	126.2	59.0	–67.1
Mean	—	–97.3	—	—	–68.3
SD ratio	—	199.5	—	—	117.0
p	—	0.04	—	—	0.014

Pre-vol (ut) = pretreatment uterine volume; Post-vol (ut) = posttreatment uterine volume; Diff. ut = difference in uterine volume before and after treatment; Pre-vol (F) = pretreatment fibroid volume; Post-vol (F) = posttreatment fibroid volume; Diff. F = difference in fibroid volume before and after treatment.

calculated as color voxels/(total voxels – background voxels), the FI as weighted color voxels/(color voxels – border voxels) and the VFI was calculated as weighted color voxels/(total voxels – background voxels).

Two consecutive doses, 4 weeks apart, of a subcutaneous injection of 3.75 mg Leuplin depot (GnRHa, Takeda, Taiwan) were given to the patients before surgery (a myomectomy). An ultrasound analysis was performed on each patient according to the following schedule: (a) before each injection, (b) before surgery, and (c) 3 consecutive months after surgery. In addition, the total blood loss during the operation was recorded.

Results

In total, 25 patients were involved in this study, but four were lost to follow-up by the end of the study. All the remaining patients ($n = 21$) received ultrasound before each injection, before the operation, and for 3 consecutive months after the operation. The mean age of the patients was 34.8 (range, 27–45) years; the mean decrease in fibroid volume, 68.3 mm^3 ($p = 0.014$); mean decrease in uterine volume, 97.3 mm^3 ($p = 0.037$); mean difference in PI, 0.19 ($p = 0.43$); mean difference in RI, 0.01 ($p = 0.87$); mean difference in VI, –4.05 ($p = 0.09$); mean difference in FI, –2.42 ($p = 0.36$); and the mean difference in VFI was –4.36 ($p = 0.04$).

The data indicated a significant decrease in uterine volume ($p = 0.039$), fibroid volume ($p = 0.014$) (Table 1), and VFI ($p = 0.049$) (Table 2); VI and FI (Table 2) seemed to decrease after GnRHa injection but not significantly, and RI and PI (Table 3) showed no difference after GnRHa injection.

Discussion

Uterine fibroids are the most common benign neoplasm in the female pelvis and occur in 20–25% of women of reproductive age. They arise mostly from the smooth muscle and soft tissue of the uterine fundus and corpus, but 3% arise from the cervix [1]. There are

Table 2. Comparison of variables between VI, FI and VFI in fibroids

Pre-VI	Post-VI	Diff. VI	Pre-FI	Post-FI	Diff. FI	Pre-VFI	Post-VFI	Diff. VFI
0.01	0.05	0.05	37.60	57.60	20.00	0.002	0.03	0.03
25.80	0.70	–25.09	68.70	41.73	–26.90	17.70	0.29	17.40
3.00	2.50	–0.51	43.00	60.48	17.48	32.90	1.56	–31.30
1.60	0.78	–0.79	69.23	66.65	–2.58	1.09	0.52	–0.57
1.60	1.08	–0.54	64.60	61.78	–2.83	1.05	0.66	–0.39
4.17	1.09	–3.08	74.60	70.60	–4.01	3.11	0.77	–2.34
3.28	1.01	–2.27	70.47	67.10	–3.38	2.31	0.68	–1.63
8.38	21.35	12.97	69.92	71.00	1.10	5.85	15.16	9.31
4.14	4.92	0.78	65.05	57.70	–7.30	2.69	2.84	0.15
8.42	13.94	5.52	68.10	65.38	–2.72	5.73	9.10	3.38
17.13	1.37	–15.76	66.34	65.88	–0.46	11.36	0.90	–10.46
15.40	0.35	–15.05	68.23	59.13	–9.10	10.50	0.21	–10.29
19.00	0.73	–18.27	70.00	63.65	–6.35	13.30	0.46	–12.84
22.70	1.45	–21.25	74.30	46.70	–27.60	16.90	0.67	–16.23
11.90	0.53	–11.37	59.63	66.88	7.25	7.15	0.35	–6.80
0.61	2.84	2.23	533.88	63.00	9.15	0.33	1.79	1.46
0.28	12.42	12.14	61.73	61.70	–0.01	0.17	7.66	7.46
2.51	1.73	–0.78	66.35	47.30	–19.10	1.66	0.82	–0.84
0.53	1.65	1.12	64.51	66.30	1.82	0.35	1.09	0.74
8.70	15.90	7.20	69.82	69.36	–0.46	6.07	11.10	5.00
20.00	7.61	–12.39	68.85	74.16	5.31	13.70	5.64	–8.00
Mean	—	–4.05	—	—	2.41	—	—	–4.36
SD ratio	—	10.60	—	—	12.89	—	—	9.56
p	—	0.09	—	—	0.36	—	—	0.05

VI = color voxels/(total voxels – background voxels); FI = weighted color voxels/(color voxels – border voxels); VFI = weighted color voxels/(total voxels – background voxels); Pre = pretreatment; Post = posttreatment; Diff. = differences.

various medical methods of management such as GnRHa, progesterone, and danazol, and surgical methods such as a hysterectomy, myomectomy, and uterine arterial obliteration. The study we designed here attempted to evaluate the response of several aspects of fibroids, especially the vascularity, to GnRHa treatment.

There are several effects of GnRHa on fibroids. Histologically, the arterioles in the myomas have significantly thicker walls, which is due to smooth muscle cell hyperplasia in the muscularis media, and this might play a role in the decreased blood flow [2]. Intramyomatous arteries are smaller and more often show arteriosclerotic changes in leiomyomas removed from women treated with GnRHa. Estrogen deprivation induced by GnRHa may cause relative vasoconstriction of the myomatous vessels. Increased cellularity and hyalinization in leiomyomata were noted following GnRH agonist treatment. GnRHa therapy suppresses cell proliferation and causes a transient increase in apoptosis in uterine leiomyomas [3]. In addition, the cellular proliferation index, ER, PR expression and the number of cycling cells decrease, and there is a relative overexpression of both collagen type I and collagen type III mRNA [4].

The vascularization on the periphery of the myoma with an RI value of 0.54 ± 0.08 was more clearly delineated, but other myomas with necrosis, inflammation, and degenerative change will give lower RI values. In addition, the uterine arteries in those with a myoma showed a lower impedance (RI of 0.74 ± 0.09) than the ones without a myoma (RI of 0.84 ± 0.09) [5]. From the view of 3D power Doppler, regular vascularity at the periphery could be detected in 84.3% of myomas [6]. Another new method of vascular quantification called a 3D histogram was reported recently. It measures the color percentage and flow amplitudes in the volume of interest. Artifacts are rather common such as tissue, patient, or probe movements because of the high sensitivity of the amplitude-based color Doppler. The parameters of 3D histograms are the VI, FI, VFI, and flow-vessel quotient (FVQ). These parameters provide values for the vessels and the intensity of flow in the tumor or tissue [7].

If the treated leiomyomata are not immediately removed surgically after therapy, rapid regrowth can occur and again cause clinical symptoms. The volume of fibroids will shrink from 30% to 40% after 2–3 doses of GnRHa, but can rebound to the same volume or

Table 3. Comparison of RI and PI values in uterine artery

Pre-RI	Post-RI	Diff. RI	Pre-PI	Post-PI	Diff. PI
0.78	0.29	–0.49	1.61	3.19	1.58
0.12	1.00	0.88	5.40	5.50	0.10
0.44	0.25	–0.19	1.48	2.57	1.09
0.22	0.39	0.17	0.92	1.07	0.15
0.90	1.00	0.10	3.06	2.59	–0.47
0.71	0.59	–0.12	1.98	2.51	0.53
0.52	0.68	0.16	1.98	1.53	–0.45
0.67	0.61	–0.06	1.11	2.23	1.12
0.45	0.35	–0.10	1.20	2.78	1.58
0.78	1.00	0.22	2.15	2.77	0.62
0.74	0.44	–0.30	1.96	1.50	–0.46
0.14	0.64	0.50	0.96	2.96	2.00
0.67	0.45	–0.22	1.96	2.39	0.43
0.81	0.64	–0.17	2.46	1.17	–1.29
0.31	0.20	–0.11	1.15	0.98	–0.17
0.23	0.69	0.46	3.94	3.05	–0.89
0.38	0.29	–0.09	1.35	0.77	–0.58
0.88	0.86	–0.02	2.20	3.63	1.43
0.80	0.38	–0.42	4.55	2.43	–2.12
0.34	0.00	–0.34	1.11	0.00	–1.11
0.62	1.00	0.38	2.70	3.57	0.87
Mean	—	0.01	—	—	0.18
SD	—	0.33	—	—	0.08
p	—	0.87	—	—	0.43

RI = resistance index; PI = pulsative index.

larger within 2–3 months after cessation of the drug. From the aspect of vascularity, statistically significant increase in RI and PI for major leiomyoma vessels were observed at the end of the 4th week, which further significantly increased after 8 and 12 weeks. These findings were directly correlated with significant decreases in estradiol levels after 4, 8, and 12 weeks [8].

The dosages and duration of GnRHa, according to the literature [9–11] and our own experiences showed that the volume of the fibroids shrank dramatically and that the total blood loss during the operation was less after two doses of GnRHa injection. Therefore, we used two doses of 3.75 mg Leuplin depot (GnRHa) 1 month apart, as a subcutaneous injection in this study. A myomectomy was performed 1 month after the last dose. In addition, it was reported that the combination of GnRHa with raloxifene induced a higher reduction in fibroid sizes.

Genetically, we used comparative genomic hybridization (CGH) to evaluate the different effects of fibroid shrinkage after GnRHa treatment. CGH can determine the site of genomic instability (by defining specific loci) and by utilizing results of the Human Genome Project (DNA sequence) for microarray detection, we were further able to detect the functional proteins from gene expression. Medical treatment of a leiomyoma may soon exist through knowledge of the function of a particular protein's expression pattern. Using this knowledge for genetic consultations may be difficult, but it is encouraging and may provide a new way to treat fibroids.

Conservative management of fibroids, which has lower morbidity and mortality, is important especially in patients who wish to retain the ability of child-bearing. Therefore, this study provides more information about the possible pathogenesis of leiomyomatous lesions from the myometrium by vascularization and together with information from CGH and the Human Genome Project, a new modality of treatment for fibroids may be possible.

From the various data shown in this study, the volume and vascularity of fibroids (including the VI, FI and VFI), and the volume of the uterus decreased significantly after two doses of GnRHa treatment. In addition, blood loss during the operation decreased significantly compared to that of an untreated group. The quantitative values (including VI, FI and VFI) of the 3D histogram did not significantly differ, possibly due to the limited number of patients.

Finally, the blood flow in the uterus and fibroids is another important parameter with fibroid shrinkage, and 3D histograms are a new and quantitative method for blood flow detection that can be used preoperatively and for the conservative treatment of fibroids.

References

1. Kurjak A, Zalud I. Uterine masses. In: Kurjak, ed. *Transvaginal Color Doppler*. Carnforth, UK: Parthenon Publishing, 1991:123.
2. Kalir T, Wu H, Gordon RE, et al. Morphometric and electron microscopic analyses of the effect of gonadotropin-releasing hormone agonist treatment on arteriole size in uterine leiomyomas. *Arch Pathol Lab Med* 2000;124:1295–8.
3. Mizutani T, Sugihara A, Nakamuro K, et al. Suppression of cell proliferation and induction of apoptosis in uterine leiomyoma by gonadotropin-releasing hormone agonist (leuprolide acetate). *J Clin Endocrinol Metab* 1998;83:1253–5.
4. Vu K, Greenspan DL, Wu TC, et al. Cellular proliferation, estrogen receptor, progesterone receptor, and bcl-2 expression in GnRH agonist-treated uterine leiomyomas. *Hum Pathol* 1998;29:359–63.
5. Kurjak A, Kupesic-Urek S, Miric D. The assessment of benign uterine tumor vascularization by transvaginal color Doppler. *Ultrasound Med Biol* 1992;18:645–8.
6. Kurjak A, Kupesic-Urek S. Three-dimensional ultrasound and power Doppler in assessment of uterine and ovarian angiogenesis: a prospective study. *Croat Med J* 1999;40:51–8.
7. Kurjak A, Kupesic S, Zodan T. *Three Dimensional and Power Doppler in the Study of Angiogenesis*. Carnforth, UK: Parthenon Publishing, 2000:15.
8. Aleem FA, Predanic M. The hemodynamic effect of GnRH agonist therapy on uterine leiomyoma vascularity: a prospective study using transvaginal color Doppler sonography. *Gynecol Endocrinol* 1995;9:253–8.
9. Kiltz RJ, Rutgers J, Phillips J, et al. Absence of a dose–response effect of leuprolide acetate on leiomyomata uteri size. *Fertil Steril* 1994;61:1021–6.
10. Giorgino FL, Cetera C. The management of leiomyoma uteri by GnRH analogues. *Clin Exp Obstet Gynecol* 1991;18:137–43.
11. Wieacker P, Geisthovel F, Adelberger V, et al. GnRH-analogs in the therapy of uterine myomatosis. *Therapeutische Umschau* 1990;47:951–7. [In German]